REMARKS

The Office Action dated January 16, 2004 has been received and carefully noted. The above amendments and following remarks are submitted as a full and complete response thereto.

Claims 1, 3, 4, 6, and 10-12 are pending. Claims 1, 3, 4, 6 and 10-12 are rejected.

By this Amendment, claim 1 is amended and new claim 24 is added. No new matter is added, and the claims are supported throughout the Specification.

Claims 1, 3, 4, 6, and 10-12 remain rejected under 35 U.S.C. § 112, first paragraph, for assertedly failing to enable one skilled in the art to make or use the invention. In making this rejection, the Office Action concedes that the claims are "enabling for a method for enhancing arteriogenesis and/or the growth of collateral arteries and/or other arteries from said collateral arteries in mammals, wherein the method comprises delivery of TGFβ1 polypeptide directly to the organ or tissue of said animals where arteriogenesis is desired." However, the Office Action contends that the claims do not "reasonably provide enablement for the method wherein the TGFβ1 is not directly delivered to the organ or tissue where arteriogenesis is desired."

The Office Action further contends that "without a mechanism to direct the TGFβ1 specifically to the target organ/tissue, one of skill in the art would not be able to reasonably expect that administering TGFβ1 to a site other than the target site would result in enhancement of arteriogenesis at the target organ/tissue without performing an undue amount of additional experimentation.

Applicants respectfully traverse the § 112, first paragraph, rejection. First, Applicants note that administration of protein is a method known in the art, and therefore, this method is inherently enabled. Additionally, Applicants note that Shire does not support the enablement rejection. Shire does not assert that the recited method in currently amended claim 1 is not possible. Rather, Shire suggests that administering protein pharmaceuticals intra-arterially is known in the art. In particular, Shire suggests that one way of overcoming potential detriments associated with the method of administration presented above is to "optimize all conditions to essentially minimize the overall impact on the protein of various degradation routes deemed to be adverse." Applicants accordingly note that since the detriments are surmountable, the method presented above is feasible. Thus, for at least the above reasons, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, of claims 1, 3, 4, 6, and 10-12 are respectfully requested.

Claim 1 remains rejected under 35 U.S.C. § 102(b) as being anticipated by Roberts et al (PNAS 1986; 83:4167-4171, "Roberts"). In making this rejection, the Office Action asserts that Roberts disclosed that subcutaneous administration of TGF-beta in newborn mice induced angiogenesis and activated fibroblasts causing formation of a granulation tissue.

Roberts discloses a method comprising an organ/tissue, the use of the TGF-beta polypeptide, and subcutaneous administration. In particular, Roberts teaches angiogenesis of small blood vessels (e.g., capillaries), particularly capillary loops.

Applicants respectfully traverse the anticipation rejection. Applicants first note that Roberts does not teach the growth of arteries, which are larger than the new blood

vessels shown in the study of Roberts. Applicants submit that there is a significant difference between arteries as claimed in the present invention, and capillaries taught in Roberts. For support, Applicants point to the statement that capillary loops "are not miniature arteries," which implies that mere size is not the only difference between arteries and capillaries. *See*, Moffett et al., Human Physiology, Second Edition, p. 399-404. Thus, Applicants submit that the blood vessels taught in Roberts are not the same as the arteries recited in claim 1. Based on the differences between arteries and capillaries, Applicants contend that evidence of growth of capillaries does not necessarily imply the same effect regarding arteries.

Moreover, Applicants note that the state of the art strictly separates angiogenesis and arteriogenesis from one another. Applicants point to several publications that support the assertion that angiogenesis and arteriogenesis (and the mechanism related to these methods) are distinguishable. *See*, Ito, WD et al., Angiogenesis But Not Collateral Growth Is Associated with Ischemia after Femoral Artery Occlusion, Am. J. Physiol., 1997, 273(3 Pt 2):H1255-65; Carmeliet, P., Mechanisms of Angiogenesis and Arteriogenesis, Nat. Med., 2000, 6(4):389-395; Arras, M. et al., Monocyte Activation in Angiogenesis and Collateral Growth in the Rabbit Hindlimb, J. Clin. Invest., 1998, 101(1):40-50; and Buschmann, I. and Schaper, W., Arteriogenesis versus angiogenesis: Two Mechanisms of Vessel Growth, News Physiol. Sci., 1999, 14:121-125. To further distinguish arteriogenesis from angiogenesis, Applicants have amended claim 1 to recite ""having preexisting arteriolar connections," thereby explicitly claiming the formation and growth of <u>arteries</u>.

Applicants also note that the present invention is distinguishable from Roberts based on TGFβ, i.e., the TGFβ used by Roberts is not the same as the TGFβ1 used in the method of the claimed invention. Applicants note that the TGFβ1 of the present invention is produced by means of a recombinant procedure, but the TGFβ of Roberts is not produced the same way. Due to the different methods of production, these two products have different properties.

Applicants have presented a number of reasons that the method taught in Roberts is not the same as the method of the presently claimed invention. Accordingly, Applicants request reconsideration and withdrawal of the anticipation rejection.

Claims 1, 4, 6 and 12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Roberts in further view of Asahara (Circulation, 1995, Vol 92, 9, Suppl., pages II365-371) (herein referred to as "Asahara"). In making this rejection, the Office Action asserts that Roberts teaches a method of inducing angiogenesis by administering a TGFβ polypeptide to a mammalian subject, but concedes that Roberts does not teach contacting the organ/tissue with a growth factor or cytokine or administering to a subject after surgical treatment that damages or destroys arteries. To make up for this deficiency, the Office Action relies on Asahara as teaching a method for inducing angiogenesis by administering a combination of two angiogenic molecules after surgical induction of unilateral hind limb ischemia.

Applicants respectfully traverse the obviousness rejection. As presented in Applicants' above argument against the anticipation rejection, Applicants respectfully submit that Roberts does not teach or suggest each of the claim elements asserted by the Office Action. Applicants note that Asahara does not make up for the numerous

deficiencies of Roberts. For instance, Asahara, like Roberts, involves angiogenesis, as opposed to arteriogenesis in the present invention. Applicants have previously discussed the fact that arteriogenesis is distinguished from angiogenesis, and this distinguishing feature (i.e., arterial growth) has been explicitly claimed in currently amended claim 1. Accordingly, for at least this reason, currently amended claim 1 would not be rendered obvious by the references, and in turn, there would be no motivation to combine the teachings of Roberts and Asahara to treat arteries with TGFβ and growth factors. Accordingly, Applicants request reconsideration and withdrawal of the obviousness rejection.

Claims 1 and 2 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Roberts in further view of U.S. Patent No. 5,482,851 to Derynck et al. ("Derynck"). In making the obvious rejection, the Office Action contends that Roberts does not "teach that the TGFβ used is recombinant TGFβ." The Office Action relies on Derynck to make up this deficiency in Roberts.

Applicants contend that this obviousness rejection appears to be an error. Claim 2 has been canceled in the previous Amendment, and therefore, this rejection is rendered moot. Accordingly, under this obviousness rejection, the Office Action has rejected claim 1 in view of the combination of Roberts and Derynck.

Applicants respectfully traverse the obviousness rejection with respect to claim 1. Applicants reassert that the presently claimed invention is distinguishable over Roberts. Applicants further assert that Derynck does not make up for the deficiencies of Roberts. Applicants note that Derynck discloses a method for producing recombinant TGFβ, and this disclosure is irrelevant with respect to claim 1. Thus, the combination of Roberts

and Derynck does not teach or suggest each and every element of the presently claimed invention. Accordingly, Applicants request reconsideration and withdrawal of the obviousness rejection.

Claims 1, 10, and 11 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Roberts in view of U.S. Patent No. 6,121,246 to Isner ("Isner"). In making this rejection, the Office Action contends that Roberts teaches the method of claim 1, but does not teach that the TGFβ is administered to a subject suffering from a vascular disease or a cardiac infarct or a stroke such as the renal artery disease like renal ischemia. The Office Action relies on Isner to make up this deficiency.

Isner teaches a method for treating ischemic tissue in a mammal by injecting an effective amount of nucleic acid capable of expressing an angiogenic protein to treat tissue having a deficiency in blood as a result of ischemic disease. Target diseases include cerebrovascular ischemia, renal ischemia, pulmonary ischemia, ischemic cardiomyopathy and myocardial ischemia.

Applicants respectfully traverse the obviousness rejection. Applicants note that the present invention is distinguishable from Isner on several grounds. Applicants note that Isner teaches a method for treating ischemic tissue in a mammal by injecting an effective amount of nucleic acid. In contrast, the present invention is concerned with the injection of protein. Thus, the combination of Roberts and Isner does not teach or suggest each and every element of the present invention. Accordingly, Applicants request reconsideration and withdrawal of the obviousness rejection.

In view of the foregoing, reconsideration of the application, withdrawal of the outstanding rejections, allowance of claims 1, 3, 4, 6 10-12, and 24, and the prompt

issuance of a Notice of Allowability are respectfully solicited.

If this application is not in condition for allowance, the Office Action is requested to contact the undersigned at the telephone listed below.

In the event this paper is not considered to be timely filed, Applicants respectfully petition for an appropriate extension of time. Any fees for such an extension, together with any additional fees that may be due with respect to this paper, may be charged to counsel's Deposit Account No. 01-2300, **referencing docket number 025896-00002.**

Respectfully submitted,

ARENT FOX KINTNER PLOTKIN & KAHN PLLC

Richard J. Berman
Attorney for Applicant
Registration No. 39,107

Customer No. 004372
1050 Connecticut Avenue, NW, Suite 400
Washington, DC 20036-5339
Telephone: (202) 857-6000

RJB/RKC/RN:ccd